

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 10/662,641  
Applicant: Standing, *et al.*  
Filed: September 15, 2003  
TC/A.AU.: Unassigned  
Examiner: Unassigned

Confirmation No.: 2664

Docket No.: 06171.105097 IDX 1021  
Customer No.: 20786  
Title:  $\beta$ -L-2' Deoxynucleosides for the Treatment of Resistant HBV Strains and Combination Therapies

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

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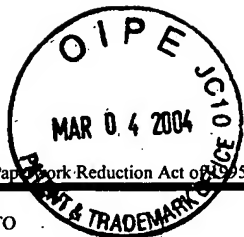
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3403759 1

**U.S. PATENT DOCUMENTS**

Examiner Initials *	Cite No. <sup>1</sup>	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code <sup>2</sup> (if known)			
	AA	4,916,122	A	Chu <i>et al.</i>	04-10-1990	
	AB	4,957,924	A	Beauchamp	09-18-1990	
	AC	5,190,926	A	Chu <i>et al.</i>	03-02-1993	
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	AAC	6,566,344	B1	Gosselin <i>et al.</i>	05-20-2003	
	AAD	6,569,837	B1	Gosselin <i>et al.</i>	05-27-2003	

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Sheet	2	of	9	Attorney Docket Number	06171.105097 IDX 1021

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		Office <sup>3</sup>	Number	Kind Code <sup>2</sup> (if known)				
	BA	EP	0,350,287	A2	Vical, Inc.	01-10-1990		
	BB	EP	0,352,248	A1	Medivir Aktiebolag	01-24-1990		
	BC	EP	0,355,131	B1	Pro-neuron, Inc.	09-04-1996		
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	BF	WO	89/02733	A1	University of California	04-06-1989		
	BG	WO	89/03838	A1	Pro-neuron, Inc.	05-05-1989		
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	BO	WO	93/00910	A1	Vical, Inc.	01-21-1993		
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	BQ	WO	94/26273	A1	Hostetler	11-24-1994		
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	BW	WO	00/09531	A2	Novirio (Idenix); CNRS	02-24-2000		
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	BY	WO	01/96353	A2	Novirio (Idenix); CNRS	12-20-2001		

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**OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS**

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	CA	AHMED, S.N.S., et al., "Early detection of viral resistance by determination of hepatitis B virus polymerase mutations in patients treated by lamivudine for chronic hepatitis B," <i>Hepatology</i> , 32(5):1078-1088 (November 2000)	
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	CG	BRIDGES, E.G., et al., "Characterization of a dCTP Transport Activity Reconstituted from Human Mitochondria," <i>J. Biol. Chem.</i> , 274(8):4620-4625 (February 19, 1999)	
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	DA	CHEN, M.S., <i>et al.</i> , "Characterization of Pyrimidine Deoxyribonucleoside Kinase (Thymidine Kinase) and Thymidylate Kinase as a Multifunctional Enzyme in Cells Transformed by Herpes Simplex Virus Type 1 and in Cells Infected with Mutant Strains of Herpes Simplex Virus," <i>J Virol.</i> , 30(3):942-945 (June 1979).	
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	DD	CUI, L., <i>et al.</i> , "Effect of Nucleoside Analogs on Neurite Regeneration and Mitochondrial DNA Synthesis in PC-12 Cells," <i>J. of Pharmacology and Experimental Therapeutics</i> , 280(3):1228-1234 (1997).	
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	EA	DUTSCHMAN, G.E., et al., "Metabolism of 2',3'-dideoxy-2',3'-didehydro-β-L-(-)-5-Fluorocytidine and Its Activity in Combination with Clinically Approved Anti-Humna Immunodeficiency Virus β-D-(+) Nucleoside Analogs In Vitro," <i>Antimicrobial Agents and Chemotherapy</i> , 42(7), 1799-1804 (July 1998).	
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	EH	HERNANDEZ-SANTIAGO, B., et al., "Pharmacology of β-L-Thymidine and β-L-2'-Deoxycytidine in HepG2 Cell and Primary Human Hepatocytes: Relevance to Chemotherapeutic Efficacy against Hepatitis B Virus," <i>Antimicrobial Agents and Chemotherapy</i> , 46(6), 1728-1733 (June 2002).	
	EI	HOARD, D.E., et al., "Conversion of Mono- and Oligodeoxyribonucleotides to 5'-Triphosphates," <i>J. Am. Chem. Soc.</i> , 87(8):1785-1788 (April 20, 1965).	
	EJ	HOLY, A., "Nucleic Acid Components and Their Analogs. CLIII. Preparation of 2'-deoxy-L-Ribonucleosides of the Pyrimidine Series," <i>Collect. Czech. Chem. Commun.</i> , 37(12):4072-4087 (1972).	
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	EL	HOSTETLER, K.Y., et al. "Greatly Enhanced Inhibition Of Human Immunodeficiency Virus Type 1 Replication In CEM And HT4-6C Cells By 3'-Deoxythymidine Diphosphate Dimyristoylglycerol, A Lipid Prodrug Of 3'-Deoxythymidine," <i>Antimicrob Agents Chemother.</i> , 36(9):2025-2029 (September 1992).	

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				Application Number	10/662,641
				Filing Date	September 15, 2003
				First Named Inventor	Standing, et al.
				Group Art Unit	1623
				Examiner Name	Unassigned
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	FA	IMAI, K., et al., "Studies on Phosphorylation. IV. Selective Phosphorylation of the Primary Hydroxyl Group in Nucleosides." <i>J. Org. Chem.</i> , 34(6):1547-1550 (June 1969).	
	FB	JONES, R.J., et al., "Mini Review: Nucleotide prodrugs," <i>Antiviral Research</i> , 27:1-17 (1995).	
	FC	JUROVČIK, W., et al., "Metabolism of pyrimidine L-nucleosides," <i>Nucleic Acids Research</i> , 3(8), 2143-2154 (August 1976).	
	FD	KORBA, B.E., et al., "A cell culture assay for compounds which inhibit hepatitis B virus replication," <i>Antiviral Res.</i> , 15:217-228 (1991).	
	FE	KRAYEVSKY, A.A., et al., "Can a Substrate Enantiomer Be a Substrate for the Same Enzyme?," <i>Molecular Biology</i> , 30(5, Part 1):585-591 (1996).	
	FF	KRAYEVSKY A.A., et al., "Should the Asymmetry of Enzymatic Active Centers Always Correlate with the Asymmetry of their Substrates?," <i>J. of Biomolecular Structure &amp; Dynamics</i> , 14(2):225-230 (1996).	
	FG	KUCERA, L.S., et al., "Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation," <i>AIDS Res. Hum. Retroviruses</i> , 6:491-501 (1990).	
	FH	LABENZ, J., et al., "Analysis of the TK Enzyme Complex Induced by HSV Types 1 and 2 by Means of Isoelectric Focusing and Polyacrylamide Gel Electrophoresis," <i>Arch. Virol.</i> , 71:235-249 (1982).	
	FI	LIN, T.-S., et al., "Synthesis and Biological Evaluation of 2',3'-Dideoxy-L-pyrimidine Nucleosides as Potential Antiviral Agents against HIV and HBV," <i>J. Med. Chem.</i> , 37:798-803 (1994).	
	FJ	LIN, T.-S., et al., "Synthesis of Several Pyrimidine L-Nucleoside Analogues as Potential Antiviral Agents," <i>Tetrahedron Letters</i> , 51(4):1055-1068 (1995).	
	FK	LIN, T.S., et al., "Design and Synthesis of 2',3'-Dideoxy-2', 3'-didehydro-β-L-cytidine (β-L-d4C) and 2',3'-Dideoxy-2', 3'-didehydro-β-L-5-fluorocytidine (β-L-Fd4C), Two Exceptionally Potent Inhibitors of Human Hepatitis B Virus (HBV) and Potent Inhibitors of Human Immunodeficiency Virus (HIV) <i>In Vitro</i> ," <i>J. Med. Chem.</i> , 39(9):1757-1759 (April 26, 1996).	
	FL	MAGA, G., et al., "Lack of stereospecificity of suid pseudorabies virus thymidine kinase," <i>Biochem. J.</i> , 294(2):381-385 (September 1, 1993).	
	FM	MANSOUR, T.S., et al., "Stereochemical Aspects of the Anti-HCMV Activity of Cytidine Nucleoside Analogues," <i>Antiviral Chemistry &amp; Chemotherapy</i> , 6(3):138-142 (1995).	
	FN	MELEGARI, M., et al., "Hepatitis B virus mutants associated with 3TC and famciclovir administration are replication defective," <i>Hepatology</i> 27(2):628-633 (February 1998).	

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	GA	NAKAYAMA, C., et al., "Synthetic Nucleosides and Nucleotides. XX. Synthesis of Various 1-β-Xylofuranosyl-5-Alkyluracils and Related Nucleosides," <i>Nucleosides &amp; Nucleotides</i> , 1(2):139-146 (1982).	
	GB	NORBECK, D.W., et al., "A new 2',3'-dideoxynucleoside prototype with <i>in vitro</i> activity against HIV," <i>Tetrahedron Letters</i> , 30(46):6263-6266 (1989).	
	GC	ONO, S. K., et al., "The polymerase L528M mutation cooperates with nucleotide binding-site mutations, increasing hepatitis B virus replication and drug resistance," <i>J. Clin. Investig.</i> , 107:449-455 (2001).	
	GD	ONO-NITA, S.K., et al., "YMDD Motif in Hepatitis B Virus DNA Polymerase Influences on Replication and Lamivudine Resistance: A Study by <i>In Vitro</i> Full-Length viral DNA Transfection," <i>Hepatology</i> , 29(3):939-945 (March 1999).	
	GE	ONO-NITA, S.K., et al., "Susceptibility of lamivudine-resistant hepatitis B virus to other reverse transcriptase inhibitors," <i>The Journal of Clinical Investigation</i> , 3(12):1635-1640 (June 1999).	
	GF	PAN-ZHOU, X.-R., et al., "Differential Effects of Antiretroviral Nucleoside Analogs on Mitochondrial Function in HepG2 Cells," <i>Antimicrobial Agents and Chemotherapy</i> , 44(3):496-503 (March 2000).	
	GG	PLACIDI, I., et al., "Cellular pharmacology of β-L-thymidine and β-L-2'-deoxycytidine in HepG2 cells and primary rat, monkey and human hepatocytes," <i>Antivir. Ther.</i> , 4(Suppl.4):46-47, abstract A122 (3 <sup>rd</sup> Int. Conf. Ther. Vir. Hepatitis) (1999).	
	GH	ROBINS, M. J., et al., "Purine nucleosides. XXIX. The synthesis of 2'-deoxy-L-adenosine and 2'-deoxy-L-guanosine and their α anomers," <i>J. Org. Chem.</i> , 35(3):636-639 (March 1970).	
	GI	ROBINS, M.J., et al., "Selective Deoxygenation and Modification at C2' of Nucleosides," <i>Nucleic Acids Research Symposium Series</i> , Vol. 11, Pages 1-4, Kyoto, Japan, November 24-26, 1982, A.E. Pritchard (ed.), IRL Press, Ltd., Oxford, England, 1982 [Chemical Abstracts Service, No. 98:10767u].	
	GJ	ROBINS, M.J., et al., "Nucleic Acid Related Compounds. 42. A General Procedure for the Efficient Deoxygenation of Secondary Alcohols. Regiospecific and Stereoselective Conversion of Ribonucleosides to 2'-Deoxynucleosides," <i>J. Am. Chem. Soc.</i> , 105:4059-4065 (1983).	
	GK	SANEYOSHI, M., et al., "Synthetic Nucleosides and Nucleotides. XIII. Stannic Chloride Catalyzed Ribosylation of Several 6-Substituted Purines," <i>Chem. Pharm. Bull.</i> , 27:2518-2521 (1979).	
	GL	SCHINAZI, R.F., et al., "Effect of Combinations of Acyclovir with Vidarabine or its 5'-Monophosphate on Herpes Simplex Viruses in Cell Culture and in Mice," <i>Antimicrobial Agents and Chemotherapy</i> , 22(3):499-507 (September 1982).	

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				First Named Inventor	Strandring, et al.
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	HA	SCHINAZI, R.F., et al., "Selective Inhibition of Human Immunodeficiency Viruses by Racemates and Enantiomers of <i>cis</i> -5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolane-5-yl] Cytosine," <i>Antimicrobial Agents and Chemotherapy</i> , 36(11):2423-2431 (November 1992).	
	HB	SEIFER, M., Hamatake R, Bifano M, Strandring DN. "Generation of replication-competent hepatitis B virus nucleocapsids in insect cells," <i>J. Virol.</i> , 72(4):2765-2776 (April 1998).	
	HC	SEIGNE' RES, B., et al., "Duck hepatitis B virus polymerase gene mutants associated with resistance to lamivudine have a decreased replication capacity in vitro and in vivo," <i>J. Hepatol.</i> 34:114-122 (2001).	
	HD	SHUTO, S., et al., "A facile one-step synthesis of 5'-phosphatidyl nucleosides by an enzymatic two-phase reaction," <i>Tetrahedron Letters</i> , 28(2):199-202 (1987).	
	HE	SÖDERLUND, J.C.F., "Mitochondrial versus cytosolic activities of deoxyribonucleoside salvage enzymes," in <i>Purine and Pyrimidine Metabolism in Man VIII</i> , A. Shota & M. Taylor (Eds.), Plenum Press, New York, 1995, pp. 201-204.	
	HF	SPADARI, S., et al., "L-Thymidine is Phosphorylated by Herpes Simplex Type 1 Thymidine Kinase and Inhibits Viral Growth," <i>J. Med. Chem.</i> , 35(22):4214-4220 (1992).	
	HG	STUYVER, L. J., et al., "Nomenclature for antiviral-resistant human hepatitis B virus mutations in the polymerase region," <i>Hepatology</i> 33(3):751-757 (March 2001).	
	HH	TYRSTED, G., et al. "Inhibition of the synthesis of 5-phosphoribosyl-1-pyrophosphate by 3'-deoxy-adenosine and structurally related nucleoside analogs." <i>Biochim. Biophys. Acta.</i> , 155(2):619-622 (February 26, 1968).	
	HI	VERRI, A., et al., "Lack of enantiospecificity of human 2'-deoxycytidine kinase: relevance for the activation of $\beta$ -L-deoxycytidine analogs as antineoplastic and antiviral agents," <i>Molecular Pharmacology</i> , 51(1):132-138 (January 1997).	
	HJ	VERRI, A., et al., "Relaxed Enantioselectivity of Human Mitochondrial Thymidine Kinase and Chemotherapeutic Uses of L-Nucleoside Analogues," <i>Biochem. J.</i> , 328(1):317-320 (November 15, 1997).	
	HK	Von JANTA-LIPINSKI, M., et al., "Newly Synthesized L-Enantiomers of 3'-Fluoro-Modified $\beta$ -2'-Deoxyribonucleoside 5'-Triphosphates Inhibit Hepatitis B DNA Polymerase but not the Five Cellular DNA Polymerases $\alpha$ , $\beta$ , $\gamma$ , $\delta$ , and $\epsilon$ Nor HIV-1 Reverse Transcriptase," <i>J. Medicinal Chemistry</i> , 41(12):2040-2046 (May 21, 1998).	
	HL	WANG, L., et al., "Recovery of Liver Sinusoidal Endothelial Cell Function over Time after Hypothermic Preservation in Rat Orthotopic Liver Transplantation," AASLD abstracts published in <i>Hepatology</i> , 24(No. 4, Pt. 2):431A, Abstract No. 1219 (1996).	

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	IA	YING, C., <i>et al.</i> , "Inhibition of the replication of the DNA polymerase M550V mutation variant of human Hepatitis B Virus by adefovir, tenofovir, L-FMAU, DAPD, penciclovir and lobucavir," <i>J. Viral Hepatitis</i> , 7:161-165 (2000).	
	IB	ZEDECK, M.S., <i>et al.</i> , "Inhibition of the steroid-induced synthesis of D5-3-ketosteroid isomerase in <i>Pseudomonas testosterone</i> by a new purine deoxyribonucleoside analog: 6-chloro-8-aza-9-cyclopentylpurine," <i>Mol. Pharmacol.</i> , 3(4):386-395 (1967).	
	IC	ZHANG, W., <i>et al.</i> , "Removal of Silyl Protecting Groups from Hydroxyl Functions with Ammonium Fluoride in Methanol." <i>Tetrahedron Letters</i> , 33(9):1177-1180 (1992).	
	ID	ZHU, Y.-L., <i>et al.</i> , "Inhibition of Replication of Hepatitis B Virus by Cytallene In Vitro," <i>Antimicrobial Agents and Chemotherapy</i> , 41(8):1755-1760 (August 1997).	
	IE	ZHU, Y.-L., <i>et al.</i> , "Anti-Hepatitis B Virus Activity and Metabolism of 2',3'-dideoxy-2',3'-didehydro-β-L-(-)-5-Fluorocytidine," <i>Antimicrobial Agents and Chemotherapy</i> , 42(7):1805-1810 (July 1998).	
	IF	ZHU, C., <i>et al.</i> , "Incorporation of Nucleoside Analogs into Nuclear or Mitochondrial DNA Is Determined by the Intracellular Phosphorylation Site," <i>J Biol Chem</i> , 275(35):26727-26731 (2000).	
	IG	ZOULIM, F., <i>et al.</i> , "Drug therapy for chronic hepatitis B: Antiviral efficacy and influence of hepatitis B virus polymerase mutations on the outcome of therapy," <i>J. Hepatology</i> , 29:151-168 (1989).	
	IH	ZOULIM, F., "Evaluation of novel strategies to combat hepatitis B virus targetting [sic] wild-type and drug-resistant mutants in experimental models," <i>Antivir. Chem. Chemother.</i> , 12(Suppl. 1):131-142 (2001).	

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